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TITLE: ^{64}Cu -DOTA-trastuzumab PET imaging in women with HER2 overexpressing breast cancer

PRINCIPAL INVESTIGATOR: Joanne Mortimer, M.D.

CONTRACTING ORGANIZATION: City of Hope Beckman Research Institute
Duarte, CA 91010

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14. ABSTRACT The assessment of HER2 by immunohistochemical staining or fluorescence in situ hybridization (FISH) is performed on breast cancer tissue and is used to determine candidacy for trastuzumab therapy. The HER2 status in recurrent cancer has been shown to change after treatment of early stage disease. Generally, tissue sampling is limited to a single tumor site and may not be representative of all sites of metastasis. Functional imaging has the potential capacity to characterize whole-tumor HER2 status for all sites of disease. We previously synthesized to 111In-DTPA-trastuzumab and used it to image patients with HER2 positive breast cancer. We have recently synthesized 64Cu-DOTA-trastuzumab and tested it in model systems. Relative to the 111In-labeled antibody, positron emission tomography (PET) with 64Cu-DOTA-trastuzumab is superior in image quality with lower radiation absorbed doses to normal tissue. We have initiated a clinical trial of 64Cu-DOTA-trastuzumab PET in women with advanced HER2 positive breast cancer. To minimize uptake of the radiotracer in normal tissues, participants will receive one of 3 "cold doses" of trastuzumab to prior to 64Cu-DOTA-trastuzumab PET. After we have determined the optimal cold dose, women with metastatic disease having varying degrees of HER2 expression will undergo 64Cu-DOTA-trastuzumab PET. We hypothesize that PET imaging will accurately characterize tumor HER2 expression and thus identify patients who are likely to benefit from trastuzumab.					
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Introduction:

HER2 is a transmembrane protein in the epidermal growth factor family with tyrosine kinase activity that results in intracellular signaling and activation of genes for cell growth and survival. Women whose cancers overexpress the *HER2* protein have a distinct natural history and are candidates for treatment with trastuzumab. The “overexpression of *HER2*” is determined on the primary tumor or a metastatic site of disease. A positive result is defined as 3+ by immunostaining for *HER2* or gene amplification. It has been suggested that individuals with *HER2* negative breast cancer may also benefit from trastuzumab therapy. Researchers at City of Hope developed a radiolabeled trastuzumab ^{64}Cu -DOTA-trastuzumab as a positron emission tomography imaging agent. The two major objectives of this research proposal were to: 1.) optimize the image quality of ^{64}Cu -DOTA-trastuzumab PET in women with advanced *HER2* positive breast cancer and 2.) assess ^{64}Cu -DOTA-trastuzumab PET uptake in women with advanced breast cancers whose tumors express *HER2* at immunostaining levels of 1+ and 2+. This DOD award provided the funding to develop ^{64}Cu -DOTA-trastuzumab as a PET imaging agent.

Body:

Task 1. IND Application and IRB approval

During the first two quarters of the grant period, we responded to questions and concerns raised by the FDA and submitted the protocol to the City of Hope Protocol Review Committee and Institutional Review Board. Once we adequately addressed the FDA queries, an IND was obtained. With the granting of an IND number, the clinical trial was submitted to the institutional review board and to the HRPO. The protocol and consent form were approved as of January 17, 2011.

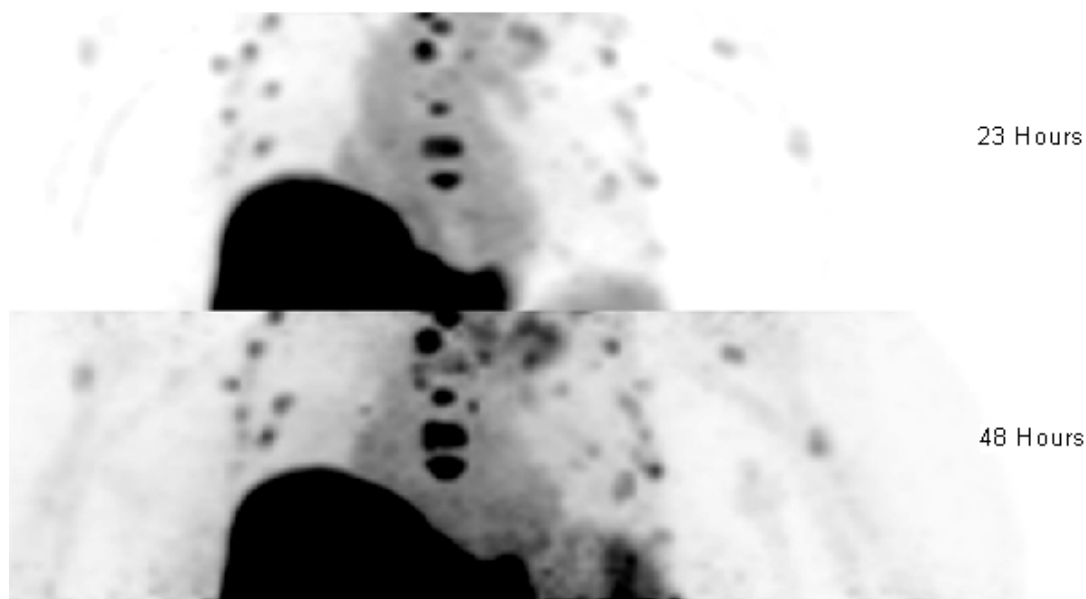
Task 2. Experiments to improve image quality

Normal tissues express *HER2*. We hypothesized that a pre-administered dose of cold trastuzumab would improve image quality and have tested 2 different doses at the time of this report. On the clinical protocol, all patients undergo biopsy confirmation of recurrent breast cancer that is *HER2* positive and an assessment of the extent of their disease. The staging workup includes an FDG-PET and bone scan to ensure that the volume and location of metastases meet the study requirements. Positron emission tomography is obtained 24 and 48 hours after injection of ^{64}Cu -DOTA-trastuzumab. The first patient was enrolled on the clinical study March 17, 2011 and as of September, 2011 five women with advanced breast cancer have undergone imaging. Three women received 5 mg of cold trastuzumab and two received 50 mg prior to the injection of the ^{64}Cu -DOTA-trastuzumab.

Our findings to date are as follows:

- Bone lesions are well visualized at 23 hours and the Day 1 images appear similar to those obtained on Day 2 (Figure 1):

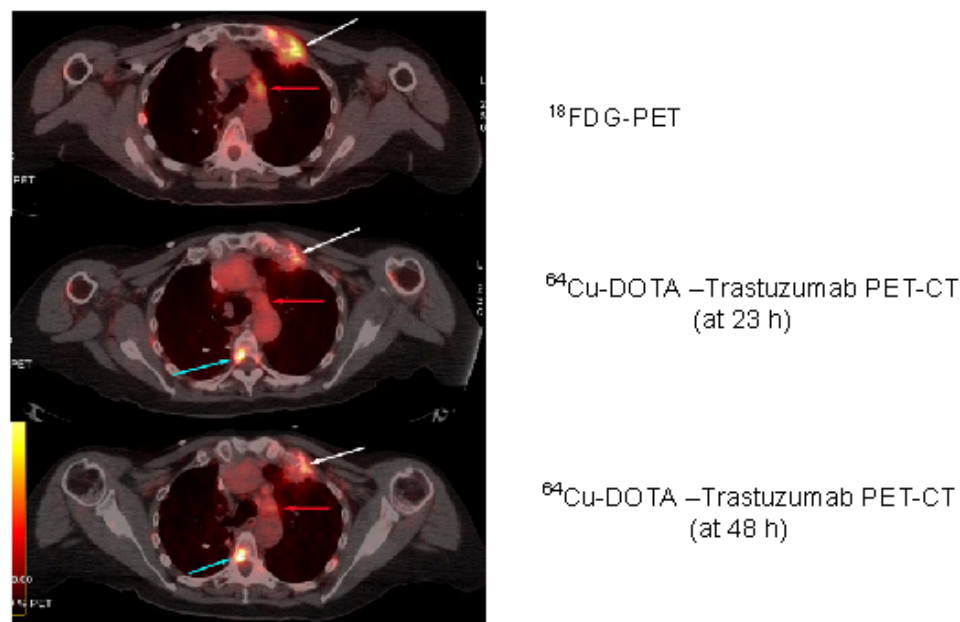
Figure 1



Numerous bone lesions are well visualized by ^{64}Cu -DOTA-Trastuzumab PET at 23 h, and the Day 1 images appear very similar to the Day 2 images.

- Lesion to non-lesion contrast improves only modestly between Day 1 and Day 2 after ^{64}Cu -DOTA –Trastuzumab injection (Figure 2)

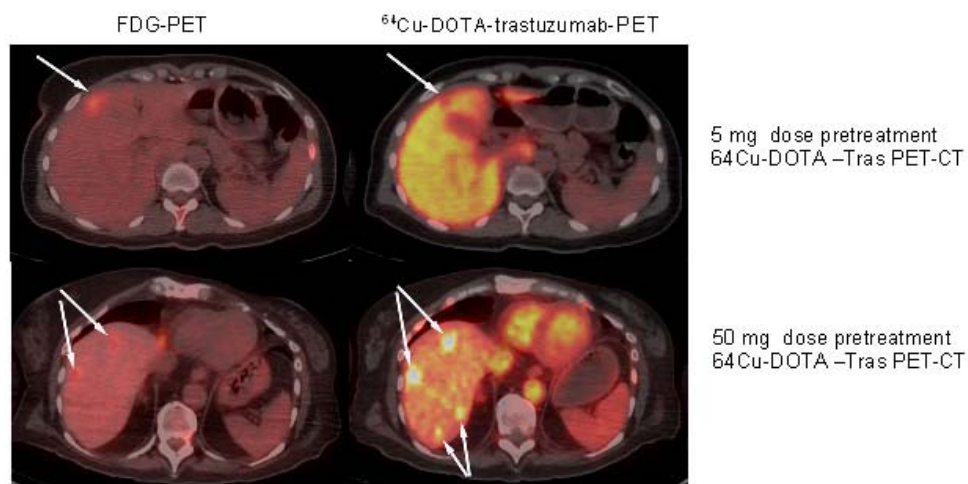
Figure 2



A lesion in the left 1st rib (white arrows) is well visualized on the Day 1 ^{64}Cu Tras PET and little changed on Day 2. A metastasis in the spine (turquoise arrows) not visualized with FDG is seen equally well on Day 1 and Day 2 ^{64}Cu Tras PET. On the other hand, a nodal metastasis (red arrows) is visualized only by Day 2 with ^{64}Cu Tras PET.

- Visualization of hepatic metastases is dramatically improved by pre-infusion of 50 mg of cold trastuzumab (Figure 3)

Figure 3



For the first patient (no added cold trastuzumab) an anterior hepatic lesion is visualized as a cold spot on ^{64}Cu -DOTA –Trastuzumab scan. Liver uptake is reduced by a factor of 3 with 50 mg of cold trastuzumab, and hepatic lesions are dramatically visualized as hot spots. For Patient 2, note that 2 lesions not seen with ^{18}F -FDG are detected with ^{64}Cu -DOTA –Trastuzumab

Key Research Accomplishments:

1. We have demonstrated the Feasibility of using ^{64}Cu -DOTA –Trastuzumab as a PET imaging agent.
2. With only five patients imaged thusfar the preadministered dose of 50 mg appears to provide improvement in image quality compared to the 5 mg dose.
3. Lesions identified on FDG-PET were also visualized on ^{64}Cu -DOTA –Trastuzumab PET.

Reportable Outcomes:

Only the Era of Hope abstract

Conclusion:

We are encouraged by the results in the first 5 patients and will continue to accrue patients to study.

References :

None

Appendices:

None

Supporting Data:

None